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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

KOZLOWSKI et al.

Serial No.: 10/727,337

Art Unit: 1711

Filed: December 02, 2003

Examiner: Asinovsky, O.

Title: METHOD FOR THE PREPARATION OF 1-BENZOTRIAZOLYL CARBONATE ESTERS
OF POLY(ETHYLENE GLYCOL)

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Samuel P. McManus, declare that:

1. The statements contained herein are provided to demonstrate the patentability of the claims pending in the above-identified patent application, U.S. Application No. 10/727,337. Claims pending in this application have been rejected in view of the asserted teachings of the primary reference, U.S. Patent No. 5,650,234 (Dolence).

2. I am currently employed as Senior Director, Product Development, Nektar Therapeutics AL, Corporation, the assignee of the subject patent application. Prior to my present position at Nektar, I held the positions of Senior Technical Director, Technical Development (2002-2003), Technical Director (2001-2002), and Consultant, Technical Development (2000-2001).

3. I received a B.S. degree in Chemistry from The Citadel in 1960, a M.S. in Chemistry from Clemson University in 1962, and a Ph.D. degree in Organic Chemistry from Clemson University in 1964.

4. I have previously held various academic positions at the University of Alabama in Huntsville including Provost and VP for Academic Affairs (1993-1994), Interim Vice President for Advancement (1994-1995), Dean, School of Graduate Studies (1989-1994), Acting Chairman, Department of Chemistry (1977-78), and Professor, Department of Chemistry (1973-2000) (list not inclusive). During the course of my career, I have supervised 29 Postdoctoral, Doctoral or Masters students.

5. I have received two Commendations by the Alabama State Senate (1990, 2000), three Certificates of Recognition by NASA (1993 (2), 1995), and am a member of various academic honor societies including Phi Kappa Phi, Alpha Epsilon Delta, and Sigma Xi.

6. I am the principal author or co-author of over 100 journal articles and books on various scientific topics, most of which relate to organic and polymer chemistry. I am a named inventor on ten issued U.S. patents or pending U.S. patent applications.

7. I am currently active in research and development related to polyethylene glycol chemistry and its applications in biotechnology, medicine, drug delivery, and the like.

8. I have carefully reviewed the contents of U.S. Patent No. 5,650,234 and the claims pending in the subject application. Claims in the present application were rejected in view of the teachings of the Dolence patent. As I understand it, it is the Examiner's view that the Applicant's claimed products appear to be the same or similar to the benzotriazolylcarbonate (BTC) products described in the Dolence patent.

9. I am aware of experiments conducted in Nektar's Huntsville laboratories in an effort to compare the PEG benzotriazolylcarbonate (BTC) ester product described in the Dolence patent ("Dolence Product") with that prepared in accordance with the teachings of the present application ("Claimed Product"). Specifically, the experiments were conducted to demonstrate a distinct chemical difference between the prior art BTC ester product of Dolence and the claimed product. The experiments summarized both in Exhibit A and Exhibit F were conducted by Nektar scientist, Xiaoming Shen.

10. As described in detail in **Exhibit A**, a PEG(3,400)di-BTC ester was prepared in accordance with the Applicant's method as embodied in claim 1. The starting material, a difunctional starting material, PEG(3,400)-diol, was converted to the corresponding PEG(3,400)di-BTC product by reaction with di(1-benzotriazolyl)carbonate rather than phosgene (as described by Dolence). The recovered product was analyzed by both ¹H NMR and size exclusion chromatography, and the results compared with those described in Example 1 of Dolence. The ¹H NMR revealed an absence of a peak at 4.28 ppm, thus indicating the lack of formation of a high molecular weight PEG carbonate impurity as reported by Dolence (**Exhibits B and C**). This result was further confirmed by size exclusion chromatography of the recovered product (**Exhibits D and E**). A comparison of size exclusion chromatograms of both the PEG(3,400)-diol starting material and the PEG(3,400)di-BTC product revealed no change in molecular weight distribution. Moreover, no high molecular weight PEG was detectable in the chromatogram. Thus, the product described by Dolence is clearly chemically distinguishable from the product produced by the method of the Applicant.

11. Further evidence in support of a distinguishable difference between the Applicant's products and those of Dolence is provided in **Exhibit F**. As described in detail in Exhibit F, an mPEG(20,000)BTC ester, a monofunctional starting material, was prepared essentially as described by Dolence (**Route 2**). Specifically, methoxyPEG_{20K} was reacted with phosgene (COCl₂) in toluene, followed by addition of hydroxybenzotriazole in base to produce the corresponding mPEG_{20K}-BTC ester. The

product was recovered by precipitation. The recovered PEG-BTC ester product composition was determined by ^1H NMR spectroscopy to possess a purity of only 90% (meaning that only 90% by weight of PEG-containing material was the desired BTC product). Further, based upon size exclusion chromatography (SEC), it was determined that the recovered PEG BTC ester product contained 4.3% by weight low molecular weight PEG-derived material – indicating the occurrence of PEG-chain cleavage. In sum, the recovered Dolence product contained only 90% PEG BTC ester product, in combination with 10% PEG-components that were not the desired PEG BTC ester. Further, the product composition also contained 4.3% by weight low molecular weight PEG components having shorter PEG chain lengths than the initial PEG starting material (MW 20,000).

CLAIMED PRODUCT: As described in detail in **Exhibit F**, a PEG BTC ester was prepared as described in the instant application, and as recited in the currently pending claims (**Route 1**). Specifically, methoxyPEG_{20K} was reacted with di(1-benzotriazolyl)carbonate in base, followed by recovery of the product by precipitation. The recovered PEG-BTC ester product was determined by ^1H NMR spectroscopy to possess a purity of 100% (meaning that 100% of the recovered PEG-containing material was product). Further, based upon SEC, it was determined that the product possessed the same molecular weight distribution as the starting material – indicating that in contrast to the Dolence product, the claimed product possessed the same or an unchanged polydispersity relative to the PEG starting material (meaning that the product lacked detectable amounts of PEG-chain cleavage/degradation products).

12. Based upon the evidence in Exhibits A-F, as summarized in the preceding sections, it is my view that the PEG BTC ester composition produced by the method of Dolence is chemically distinguishable from the PEG BTC ester product claimed by the Applicant and prepared by the method recited in the instant claims, since the chemical composition of the two products differs. Specifically, the Dolence product contains a high molecular weight PEG carbonate impurity that is not present in products produced by the Applicant's method. Further, as exemplified with the 20,000 dalton PEG

comparative example in Exhibit F, end-products produced by the two different methods differed in both percent substitution at the PEG-OH terminus (90% versus 100%) and molecular weight distribution.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; further, that these statements were made with the knowledge that willful false statements or the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Samuel P. McManus, Ph.D.

Date: _____